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Adding Mirabegron to Solifenacin to Treat Overactive Bladder Has Little Impact on Postvoid Residual Volume or Urinary Retention Risk

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Urinary retention is a complex and important urologic health issue that describes the inability to completely empty the bladder.[1] The sudden inability to void is termed acute urinary retention, which is usually accompanied by pain and severe urgency, and can have serious consequences if untreated.[2] Occasionally, acute urinary retention may be precipitated by an event such as infection or medication; thus, the definition is further subdivided into precipitated or spontaneous.[1] Chronic urinary retention describes the persistent inability to completely empty the bladder and is usually painless and imperceptible to the patient.[3]

The majority of epidemiologic data on urinary retention relates to acute urinary retention in older male patients due to its association with benign prostatic enlargement (BPE), and because clinically significant symptoms requiring medical attention are more likely to be reported than chronic urinary retention, which is often unperceived by the patient. In men aged 40–83 years, the overall incidence of acute urinary retention is 4.5-6.8 per 1000 men per year,[4,5] many times higher than in women (7 per 100,000 general population per year).[6] Incidence also increases with age, affecting eight times as many men aged 70-79 years than those aged 40-49 years.[2] The etiology of acute urinary retention can be classified into 3 categories: mechanical or dynamic obstruction (eg, BPE or drugs that increase smooth muscle tone), impaired neurologic coordination of voiding (eg, pelvic surgery or spinal injury), and bladder overdistension (eg, drugs or excessive alcohol that inhibit bladder contractility).[7,8]

Consequences of urinary retention include impaired quality of life, deterioration in the upper urinary tract function due to chronic excessive bladder pressure, and recurrent urinary tract infections and bladder calculi, which result from stagnated urine.[9] Management of acute urinary retention usually requires catheterization to empty the bladder and to alleviate symptoms.[8]

In patients with overactive bladder (OAB), the American Urological Association and the Society of Urodynamics, Female Pelvic Medicine, & Urogenital Reconstruction recommend the measurement of postvoid residual (PVR) urine volume via catheterization or bladder ultrasound scan, where there is a history of or risk factors associated with urinary retention (ie, voiding symptoms, history of incontinence or prostatic surgery, and neurologic diagnoses).[10] A PVR volume of <50 and <100 mL signifies adequate bladder emptying in the general population and the elderly population, respectively; a PVR volume of >200 mL is considered abnormal.[11] Unfortunately, PVR volume is associated with large intrapatient variability, and only extreme values (>500 mL) appear to be predictive of acute urinary retention.[6] In clinical practice, patients with suspected incomplete bladder emptying are managed according to the severity of the PVR volume and the suspected or identified etiology. For example, at the Department of Urology, Karolinska University Hospital-Huddinge, Sweden, before being discharged from the hospital, inpatients with, or suspected of, impaired bladder emptying undergo a bladder ultrasound scan immediately after emptying their bladder and are managed according to 1 of 4 categories of PVR volume: (1) 100-150 mL, follow-up bladder scan after

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3 hours; (2) 150-300 mL, follow-up bladder scan after 2 hours; (3) 300-400 mL, follow-up bladder scan after 1 hour; and (4) >400 mL, bladder to be emptied using clean intermittent catheterization or a permanent catheter according to the physician (personal communication between Dr. Aino Fianu-Jonasson and Dr. Tareq Alsaody, November 2016).

In clinical trials, it is important to identify potential dose-related increases or clinically relevant changes in the PVR volume following treatment with medications that have the potential to increase the risk of urinary retention. In the case of OAB, pharmacotherapies used to inhibit bladder contractility or to induce bladder relaxation during the storage phase could, in theory, potentially increase the risk of urinary retention. These include antimuscarinics (eg, solifenacin and tolterodine), β_3-adrenoceptor agonist (mirabegron), and the intravesical therapy onabotulinumtoxinA.[7,12] Patients most at risk may include the elderly, who are more likely to have reduced bladder contractility, pre-existing comorbidities, and concomitant medications that reinforce detrusor relaxation; others at risk include men with pre-existing bladder outlet obstruction and patients with a history of excessive PVR volumes.[6,7] The rate of acute urinary retention reported with OAB medications varies from ~8% with onabotulinumtoxinA[12] to less than 1% with antimuscarinics and mirabegron[13]; nevertheless, there is still a perception among physicians of an increased risk with antimuscarinics in male patients, which is often attributed to their mode of action.[14]

In 12-week placebo-controlled trials, mirabegron and tolterodine extended release (ER) were associated with placebo-like changes in the PVR volume (−0.9 mL [mirabegron 50 mg], −1.6 mL [placebo], and +0.1 mL [tolterodine ER 4 mg]), and the incidence of urinary retention was negligible (0.1% [mirabegron 50 mg], 0.6% [tolterodine ER 4 mg], and 0.5% [placebo]).[13] In high-risk cohorts such as male OAB patients with obstructive symptoms, urodynamic parameters are unaffected and acute urinary retention remains low following monotherapy or combination treatment. In 127 men with OAB and bladder outlet obstruction, the maximum urine flow rate (Q_{max}) and detrusor pressure at Q_{max} ($P_{det\text{-}Qmax}$) were comparable between patients treated with mirabegron 50 mg and placebo. The change from baseline to end of treatment (EoT) in Q_{max} was 0.07 and −0.33 mL/s, and the changes in $P_{det\text{-}Qmax}$ were −3.03 and 2.92 cmH_2O with mirabegron 50 mg and placebo, respectively. The increase in PVR volume was higher following treatment with mirabegron 50 mg vs placebo (~18 mL vs 0.5 mL) but remained clinically insignificant, as reflected by the solitary case of acute urinary retention in the placebo group.[15] Similar low rates of acute urinary retention (<1.0%) have been reported following a combination of mirabegron or antimuscarinic plus the alpha-blocker tamsulosin in male patients with lower urinary tract symptoms.[16,17] Treatment differences in urodynamic parameters have been reported in female OAB patients (n = 40) treated with solifenacin 5 mg or mirabegron 50 mg for 12 weeks, who had a PVR volume of <100 mL at baseline. Although similar improvements in storage-phase parameters such as bladder capacity and detrusor overactivity were observed, solifenacin had a detrimental effect on voiding-phase parameters compared to mirabegron. The Q_{max}, opening detrusor pressure ($P_{det\text{-}open}$), and $P_{det\text{-}Qmax}$ decreased significantly, whereas the PVR volume increased significantly with solifenacin 5 mg (+3.28 mL, P = .0139). In contrast, Q_{max}, $P_{det\text{-}open}$, and $P_{det\text{-}Qmax}$ all increased without significance and the PVR volume was moderately reduced without significance with mirabegron 50 mg (−1.13 mL).[18] Despite the statistically significant changes in voiding parameters with solifenacin, the increase in the PVR volume was not clinically significant. The study was limited by the small patient population but illustrated the opposing actions of both drug classes on voiding function and the propensity to retain urine. However, these opposing actions on voiding mechanics do not appear to translate into clinically meaningful differences at 12 weeks or longer. After 12 months of treatment with mirabegron 50 mg or tolterodine ER 4 mg, the rate of urinary retention remained low (n = 1 [0.1%] mirabegron 50 mg vs n = 3 [0.4%] tolterodine ER 4 mg), and one case of acute urinary retention was reported with tolterodine, which required discontinuation of the drug.[19]

The distinct mechanisms of action that distinguish mirabegron from antimuscarinics suggest that their use in combination could have an additive or synergistic inhibitory effect on bladder contractility and urinary retention risk. Herein we report PVR volumes and urinary retention rates in OAB patients treated with a combination of an antimuscarinic (solifenacin) and mirabegron in the BESIDE study (NCT01908829).

The BESIDE study investigated the efficacy and safety of add-on mirabegron 50 mg to solifenacin 5 mg (combination) vs solifenacin monotherapy (5 or 10 mg) for 12 weeks, in refractory incontinent OAB patients after an initial 4-week dose of solifenacin 5 mg. Combination treatment provided greater improvement in OAB symptoms and patient-reported outcomes vs solifenacin monotherapy, and was well-tolerated.[20,21] The PVR volume was assessed by bladder ultrasound scan at each visit and was summarized according to absolute change and shift to 1 of 3 categories (≥0 to <150 mL, ≥150 to <300 mL, ≥300 mL) from baseline to EoT. Increases in the PVR volume from a baseline value of <150 mL to a PVR volume of >250 mL were queried for clinical significance; treatment-emergent adverse events (TEAEs) for urinary retention were based on spontaneous reporting using a predefined list of preferred and lower-level terms.[20] The mean baseline PVR volume ranged from 23 to 26 mL across the treatment groups. Patients with a PVR volume of >150 mL were excluded from the study. At EoT, small, clinically insignificant increases in the PVR volume were observed with combination treatment (5.5 mL), solifenacin 5 mg (3.0 mL), and solifenacin 10 mg (7.4 mL). Approximately 97% or more of patients in any treatment group had no shift in the PVR volume to a higher category from baseline to EoT (Fig. 1). Increased residual urine volume was reported as a TEAE in 6 patients (combination treatment, n = 2 [0.3%]; solifenacin

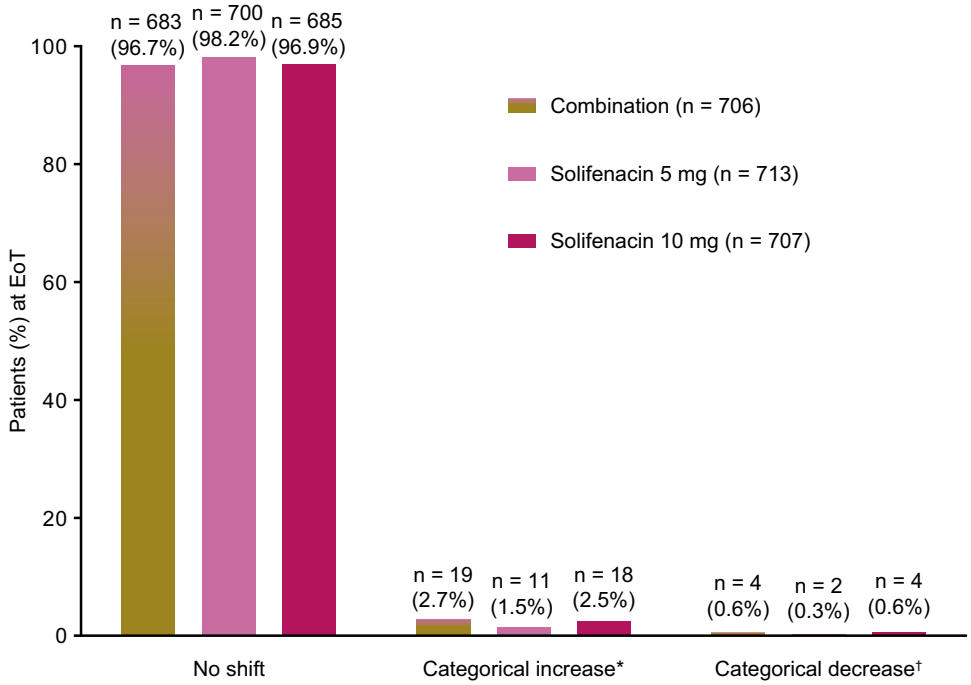

Figure 1. Shift in PVR volume from baseline to EoT. *Baseline ≥0 to <150 L increased to ≥150 to <300 mL or to ≥300 mL, or baseline ≥150 to <300 mL increased to ≥300 mL; †baseline ≥150 to <300 mL decreased to ≥0 to <150 mL or baseline ≥300 mL decreased to ≥150 to <300 mL or decreased to ≥0 to <150 mL. EoT, end of treatment.

5 mg, n = 2 [0.3%]; and solifenacin 10 mg, n = 2 [0.3%]), and urinary retention was reported as a TEAE in 8 patients (combination, n = 2 [0.3%]; solifenacin 5 mg, n = 1 [0.1%]; solifenacin 10 mg, n = 5 [0.7%]). Two patients in the solifenacin 10 mg group discontinued treatment due to urinary retention, but there were no cases of acute urinary retention or patients requiring catheterization in any treatment group.

The magnitude of the change in the PVR volume and rates of urinary retention after 12 weeks in the BESIDE study is consistent those in other 12-week studies that have investigated various doses of mirabegron (25 or 50 mg) and solifenacin (2.5, 5.0, or 10.0 mg) in combination.[22-24] In a phase II, dose-ranging study including 1306 OAB patients, the highest reported mean increase in PVR volume was 13.9 mL in the solifenacin 10 mg-mirabegron 50 mg group; 1 case of acute urinary retention was reported in the solifenacin 2.5 mg-mirabegron 25 mg group.[22] In a phase III study in 223 Japanese OAB patients, the highest mean increase in PVR volume was 8.0 mL in the solifenacin 5 mg-mirabegron 25 mg group, and there were no cases of urinary retention.[23] In the SYNERGY study (NCT01972841), which compared solifenacin 5 mg-mirabegron 25 mg or 50 mg vs solifenacin or mirabegron monotherapy or placebo in 3527 OAB patients, the highest change in the mean PVR volume was 11 mL in the solifenacin 5 mg-mirabegron 50 mg group; there were 4 cases of urinary retention requiring catheterization (solifenacin 5 mg-mirabegron 25 mg, n = 2, and solifenacin 5 mg-mirabegron 50 mg, n = 2), which was considered acute urinary retention in 1 patient treated with solifenacin 5 mg-mirabegron 50 mg.[24]

The BESIDE study suggests that combining 2 distinct classes of oral pharmacotherapy (antimuscarinic and β_3-adrenoceptor agonist) to treat OAB has a negligible effect on the PVR volume and urinary retention risk. The coadministration of solifenacin 5 mg and mirabegron 50 mg may be a reasonable alternative to a dose escalation to solifenacin 10 mg, without compromising bladder contractility during the voiding phase, as demonstrated by the absence of clinically relevant changes in the PVR volume. Study limitations included the relatively small male cohort (approximately 25% of the overall population), which is an inherent problem in OAB trials, and the low proportion of patients, ~ 30% and ~8%, respectively, over the age of 65 and 75 years, who are potentially more susceptible to urinary retention or increases in PVR volume.

In clinical practice, the routine assessment of residual urine is recommended in high-risk cohorts such as elderly men (>75 years) with BPE, patients with a history of elevated PVR volumes (>200 mL), and patients with OAB receiving oral pharmacotherapy as monotherapy or combination therapy who develop voiding symptoms. Further studies are recommended to improve our understanding of the relationship between PVR volume and urinary retention, and to explore predictive factors in the male and female OAB population. It is important to recognize that the inclusion and exclusion criteria employed in phase III clinical trials minimize the number of patients with a history or high risk of urinary retention. Observational and noninterventional studies are more reflective of real-life clinical practice and are recommended as a means of assessing the efficacy and safety of OAB medications in higher-risk cohorts.

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